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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY-DOCKET NO.	CONFIRMATION NO.
09/510,562	02/22/2000	Gerard Housey	395/35	3061

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KENYON & KENYON
ONE BROADWAY
NEW YORK, NY 10004

[REDACTED] EXAMINER

GUZO, DAVID

[REDACTED] ART UNIT [REDACTED] PAPER NUMBER

1636

DATE MAILED: 11/19/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/510,562	HOUSEY, GERARD
	Examiner David Guzo	Art Unit 1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 13 August 2002.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 33,34,36,37,43-50,59-65 and 71-78 is/are pending in the application.
 - 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 33-34, 36-37, 43-50, 59-65, 71-78 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 - a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input checked="" type="checkbox"/> Interview Summary (PTO-413) Paper No(s). <u>28</u>
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>27</u>	6) <input type="checkbox"/> Other: _____

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Detailed Action

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 33-34, 36, 43-44, 46, 47, 49, 63, 64, 71-72, 74-75 and 77 are rejected under 35 U.S.C. 102(b) as being anticipated by Drebin et al.

This rejection is maintained for reasons of record in the previous Office Action (mailed 2/4/02) and for reasons outlined below.

Applicant traverses this rejection by asserting that Drebin et al. does not anticipate the claimed invention because the claimed invention relates to inhibitors and activators of enzymatic activity, not antibodies. Applicant asserts that antibodies are generally thought of as binding proteins and not inhibitors or activators of enzymes. Applicant asserts that the FDA distinguishes between chemical agents and biological agents (such as antibodies) and assigns each to separate divisions of the FDA. Applicant also cites several references which applicants assert provide support for the argument that "chemical agents" do not encompass antibodies.

Applicant also asserts that even if one construes that antibodies are encompassed within the meaning of the term "chemical agents", Drebin et al. does not anticipate the claimed invention

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because Drebin et al. does not teach cells that exhibit a phenotypic characteristic that is responsive to the inhibition or activation of the target enzyme and do not teach use of cells that exhibit a responsive phenotypic characteristics other then the level of the target enzyme.

Applicant argues that their statements with regard to the teachings of Drebin et al. are consistent with statements by the Opposition Division of the EPO. Finally, applicant asserts that the ordinary skilled artisan would take Drebin et al. as evidence that the effects of overproduction of a membrane protein in a cell can be eliminated by an agent (antibody) that destroys the overproduced protein, thereby returning the cellular phenotype to the unaltered state. In contrast, applicant asserts that the antibodies disclosed by Drebin et al. do not affect the enzymatic activity of the receptor according to applicants' method.

Applicant's response filed 8/13/02 has been carefully considered but are not persuasive. With regard to applicant's arguments that antibodies would not be considered by the skilled artisan to be inhibitors or activators of enzyme activities, it is noted that antibodies (which can be considered as chemical agents) can serve, as noted by Drebin et al., as agents which directly interact with (bind to) and inhibit the activity of the target enzyme. The fact that some people generally consider antibodies to be binding proteins does not negate the fact that antibodies can, as noted by Drebin et al., also serve as inhibitors of a target cellular protein. With regard to applicant's assertions concerning the distinctions between 'chemical agents' and biological

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agents such as antibodies, applicant's specification makes no such differentiation between chemical agents and biological agents such as antibodies. With regard to the FDA distinguishing between chemical agents and biological agents, it is noted that the FDA makes no such distinction. The handling of chemical agents by one division of the FDA and biological agents by another division appears to be more a matter of how jurisdictional boundaries within the FDA are organized and not a matter of a fundamental distinction between chemical agents and biological agents. With regard to the references cited by applicant, said references do not make a distinction between "chemical agents" and biological agents such as antibodies; instead the references merely use various agents for various purposes. For example, Perussia et al.(cited by applicant) use some agents to induce differentiation and use other agents (antibodies) for monitoring the presence of differentiation antigens. Perussia et al. provide no definition of "chemical agents" which would exclude biological agents such as antibodies.

With regard to applicant's assertion that Drebin et al. does not teach cells which exhibit a phenotypic characteristic that is responsive to the inhibition or activation of the target enzyme, it is again noted that Drebin et al. teaches a phenotypic characteristic (transformed phenotype) in NIH-3T3 that is responsive to antibody mediated inhibition of the target enzyme (the neu-oncogene p185). With regard to applicant's arguments that Drebin et al. teaches the removal of the enzyme (rather than inhibiting or activating the enzyme), it is noted that the pending claims

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do not exclude the binding and internalization (within the cell) of the target enzyme by the agent in the context of inhibiting the activity of the enzyme. Also, as in other given inhibitors of enzymes, removal of the antibody from the culture medium results in the reappearance of the enzyme and transformed phenotype.

Finally, with regard to the Statements of the Opposition Division of the EPO, said opinions are not binding on the U.S. Patent Office. However, the Opposition Division's indication that the "...antibody-mediated down modulation of cell surface p185 does not result in inhibition of a given target protein as defined in the patent" is problematic given the instant specification. Specifically, on p. 13 of the specification, applicant indicates that "inhibitors" include any substances which reduce or nullify entirely the activity of the target enzyme (or POI). Clearly the use of antibodies by Drebin et al. reduce or nullify the activity of the target p185 gene product.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 33-34, 36-37, 43-50, 59-65 and 71-78 are rejected under 35 U.S.C. 112,

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first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained for reasons of record in the previous Office Action and for reasons outlined below.

Applicant traverses this rejection by asserting that the specification coupled with information known in the art would provide the skilled artisan all that was needed to practice the claimed invention. Applicant asserts that assays to detect simple binding of chemical agents to proteins or enzymes were commonly used prior to the instant invention and the skilled artisan would have known how to use said assays. Applicant points to the example in the specification (on pp. 31-32) involving a cell assay for assessing the binding of a phorbol ester (PDBU) in cell lines that express differing amounts of the beta-1 isoform of PKC as an example of the binding assays which would have been well known to the skilled artisan.

Applicant traverses the rejection by indicating that although the scope and nature of the invention are broad, one of skill in the art would know how to practice the full scope of the invention given the literature cited in applicant's arguments and in the specification. With regard to the examiner's citation of the paper by Hsiao et al., applicants assert that Hsiao et al. did not use an assay system as set forth in the instant application. Applicant states that Hsiao et al. is not

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applicable to the instant invention because Hsiao et al. does not recite a specific association between the level of the target protein and the corresponding responsive change in a phenotypic characteristic elicited by the presence of the target protein in the cell.

Applicant's arguments have been considered but are not persuasive. With regard to applicant's arguments concerning the well known nature of assays to determine binding of chemical agents to proteins or enzymes, it is noted that the instant claims require that the skilled artisan determine whether a chemical agent (which may or may not interact in some fashion with the target enzyme) **interacts directly with the target enzyme** and that said **direct interaction evokes a phenotypic change** in the cells comprising the expressed enzyme compared to cells which do not express or express at a lower level, the same enzyme. Clearly, the preamble of the instant method claims requires, *a priori*, knowledge concerning the direct interaction between the test chemical agent and the target enzyme. Applicant provides no protocol for determining whether an unknown agent will interact directly with the target enzyme and whether this interaction alone will evoke a change in the phenotype. Prior art assays using intact cells are often merely preliminary screening assays to determine if a given chemical agent has some effect on a given target or metabolic pathway. Subsequent research is often required to determine what type of interaction between the test chemical agent and the target protein actually occurs. With regard to the examples cited by applicants in the specification, said examples appear to involve

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use of known test chemical agents which were known to directly interact with the target enzyme or protein.

With regard to applicant's arguments concerning the broad nature of the instant claims and the ability of the skilled artisan to rely on the prior art to perform assays to determine whether the test chemical agent directly interacts with the target enzyme, it is noted that since this is an essential step in applicant's invention, this teaching must be supplied in the specification and applicant cannot rely on the knowledge of one skilled in the art to supply the missing teachings (See *Genentech v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1997). With regard to the teachings of Hsiao et al., it is noted that Hsiao et al. recites an assay system in which expression of the c-Ha-ras oncogene (carried on plasmid pT24) results in a change in phenotype (transformed phenotype) and that addition of chemical agents such as TPA enhances this effect. Hsiao et al. notes that the mRNA levels of c-Ha-ras were increased in the transformed cells treated with TPA, thus establishing a responsive phenotypic change resulting from an activation of the c-Ha-ras oncogene. With regard to applicant's argument that transformation appears to be dependent upon the retention of enhancer sequences adjacent to the c-Ha-ras coding sequence in pT24, it is unclear what point applicant is attempting to make. The enhancer sequences appear to be a normal part of the c-Ha-ras oncogene sequence required for expression of said sequence. Contrary to applicant's arguments, Hsiao et al. demonstrates that there is a specific association

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between the level of the c-Ha-ras (as measured by increased mRNA levels, which generally results in increased levels of protein production, absent evidence to the contrary) and a corresponding change in a phenotypic characteristic (increased number of transformed cells) evoked by the presence of the protein in the cells. Additionally, if Hsiao et al. had used the exact instantly recited system, applicant has provided no evidence to contradict the examiner's assertion that the skilled artisan would have erroneously concluded that compounds such as TPA directly interacted with the c-Ha-ras oncogene product and would be activators of said product.

5. Claims 33-34, 36-37, 43-50, 59-65 and 71-78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is maintained for reasons of record in the previous Office Action and for reasons outlined below.

Applicant traverses this rejection by again asserting that the instant invention functions by looking for an increase in a phenotypic change which becomes greater with increasing expression of the POI so that inhibitors or activators of the POI can be distinguished from agents which interact with other cellular components to effect phenotypic changes. With regard to PKC,

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applicant asserts that the disclosed cell lines are sensitive and responsive to agents which inhibit or activate PKC and applicant indicates that they provide the first evidence that tamoxifen is capable of inhibiting the cellular functioning of the beta-1 isoform of PKC. Applicant indicates that their method is an improvement over prior art assays in that one of skill in the art could expect to identify substances which are inhibitors or activators of the POI and that any false positive results which may arise would be exceptional. Finally, applicant indicates that it is within the skill of the skilled artisan to determine (if desired) if the chemical agent identified by the method is indeed interacting directly with the POI.

Applicant's arguments have been considered but are not persuasive. It is again noted that the instant claims require, and are limited to, "A method of determining whether a chemical agent **that directly interacts with an enzyme** (emphasis added) is an inhibitor or activator of that enzyme...". Therefore, contrary to applicant's assertion, the skilled artisan does not have the option of determining if the chemical agent identified by the method directly interacts with the POI and the absence of a disclosure on how the skilled artisan would do this for any given target enzyme would force the skilled artisan to conclude that applicant was not in possession of the claimed invention. With regard to applicant's arguments concerning the graded responses to inhibitors or activators, it is noted that indirect interactions between the chemical agent and POI can produce the same results. For example, if the chemical agent to be tested interacted with a

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protein or enzyme which in turn inhibited or activated the POI to the extent that said POI is present in the cell, a response similar to that observed if the test chemical agent interacted directly with the POI would be seen. With regard to applicant's assertions regarding tamoxifen and PKC, it is noted that tamoxifen was a known inhibitor of PKC in a cell-free assay and it is unknown if tamoxifen interacted directly with the PKCs expressed on the cells used in the instant assay. Again, without knowing beforehand whether a given chemical agent is an inhibitor or activator of a given enzyme and without knowing beforehand whether said chemical agent interacts directly with the target enzyme, it is unclear how the instant disclosure would allow the skilled artisan to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33-34, 36-37, 43-50, 59-65 and 71-78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is maintained for reasons of record in the previous Office Action and for reasons outlined below.

Applicant traverses this rejection by asserting that the skilled practitioner would understand

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that the control cell line would not be “vastly different” from the test cell but should be as similar as possible to avoid difficulty in analyzing results. Applicant indicates that the method is applicable as long as the phenotypic characteristic affected by expression of the protein of interest is detectable and the effect of the inhibitor or activator is greater on the higher producing cell line.

Applicant’s arguments have been considered but are not persuasive. It is unclear how closely related the two cell lines need to be in order to avoid “...difficulty in analyzing results.” It would seem that the control cell line would need to be chosen empirically based upon the choice of the target enzyme and the effects of expression of said target enzyme on the cell line chosen.

Applicant provides no teachings sufficient to clarify how different the control cell can be from the test cell.

With regard to the “second genetic vector”, applicant argues that the skilled artisan would understand that the second vector should otherwise be as similar as possible to the first vector; however, the difference in phenotypic characteristic relied upon for identification of inhibitors or activators should result from differential expression of the protein of interest. Otherwise, differences between the first and second vectors are not excluded.

In response, the examiner notes that the metes and bounds of the claimed subject matter are still unclear. Applicant’s stating that the skilled artisan would know what differences in the

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genetic vector should be avoided does not provide guidance on how similar the vectors can be. It can be assumed that the components of vectors (excluding the gene encoding the POI) used would need to be determined in a case by case basis depending on the cell lines used in each individual test because host cell-vector combinations with regard to vector promoters, other expression regulatory elements, selection markers, etc. need to be determined empirically.

No Claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate .

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Faxes may be sent directly to the examiner at (703) 746-5061.

Any inquiry of a general nature or relating to the status of this application or proceeding or relating to attachments to this Office Action should be directed to Patent Analyst Zeta Adams, whose telephone number is (703) 305-3291.

David Guzo
November 2, 2002

DAVID GUZO
PRIMARY EXAMINER
